44. The method of claim 37, wherein said neurodegenerative disorder is selected from the group consisting of degeneration of cells in the spinal cord, physical deterioration, death of spinal cord cells, abnormal pattern of spinal cord cells, amyotrophic lateral sclerosis, multiple sclerosis, syringomyelia, spinal tumors or metastasis, bacterial spinal cord infections, and parasitic spinal cord infections.

45. The composition of claim 1, wherein the spinal cord cell is isolated from an embryonic pig at a gestational when isolated spinal cord cells have 50% or greater viability.

46. The method of claim 18, wherein the spinal cord cell is isolated from an embryonic pig at a gestational when isolated spinal cord cells have 50% or greater viability.

47. The composition of claim 1, wherein the composition comprises a population of isolated spinal cord cells in which at least about 30% of the spinal cord cells have neuron morphology.

REMARKS

Claims 1-8, 10-26, and 28-47 were under examination in the present application. Claims 2 and 19 have been canceled without prejudice herein. Claims 1, 3, 4, 10, 18, 20, 21, and 36 have been amended. Accordingly, claims 1, 3-8, 10-18, 20-26, and 28-47 are presently under examination. Support for the amendment to claims 1 and 18 can be found, e.g., at page 9 of the specification.

Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. Amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in this or in another patent application.

No new matter has been added. Claim 10 has been amended to correct a grammatical error. Claims 3, 4, 20, 21, and 36 have been amended to change claim dependency. Claims 1 and 18 have been amended to require that the cells be from an embryonic pig and to incorporate gestational age limitations. Therefore, the above amendments raise no new issues which would require further consideration and/or search by the Examiner. Furthermore, in view of the amendments and arguments set forth herein, the number of issues for appeal have been reduced.

Rejection of Claims 1-4, 17-21, 36, 39-45 and 47 Under 35 U.S.C §103(a)

Claims 1-4, 17-21, 36, 39-45 and 47 are rejected under 35 U.S.C. §103(a) as being unpatentable over Giovanini *et al.* in view of Galpern *et al.* The Examiner cites Giovanini *et al.* as teaching "that human fetal spinal cord cells can be isolated and used in a method of treating a mammalian xenogeneic subject having spinal cord damage." The Examiner relies upon Galpern *et al.* as providing motivation "for substituting human fetal spinal cord cells with porcine cells." According to the Examiner, Galpern *et al.* "teach the lack of availability of human fetal tissue, [and] the difficulties of storing human fetal tissue." The Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143.*** The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the

applicant's disclosure." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

The pending claims are directed to compositions for transplantation into a mammalian xenogeneic subject comprising isolated spinal cord cells ***obtained from an embryonic pig of between about 24 and about 35 days of gestation***, such that treatment of spinal cord damage that would benefit from survival and integration of the spinal cord cells is obtained upon transplantation into the subject. The pending claims are further directed to methods of treating a mammalian xenogeneic subject having spinal cord damage that would benefit from survival and integration of porcine spinal cord cells by administering to the subject a composition comprising isolated spinal cord cells ***obtained from an embryonic pig of between about 24 and about 35 days of gestation***, such that treatment of spinal cord damage is obtained upon administration of the composition to the subject.

In response to the Applicant's previous assertion that there is no motivation to combine these two references to arrive at the claimed invention, the Examiner states that

> ...the teachings of Galpern *et al.* indicate that porcine neurons can be used to reconstruct neuronal circuitries in vivo. Thus, one of ordinary skill in the art would have been motivated to isolate and use an alternative source of fetal spinal cords cells to treat spinal cord diseases/injuries, and would have had a high expectation of successfully treating the subject in need thereof with porcine fetal spinal cord cells in view of the teachings of the combined references.

Applicant maintains that one skilled in the art would not have been motivated to combine Giovanini *et al.* and Galpern *et al.* to arrive at the claimed invention.

Giovanini teaches the use of spinal cord cells from a human fetus to treat chronic contusion. Galpern *et al.* teaches neurotransplantation of ***porcine dopaminergic neurons isolated from fetal ventral mesencephalons*** to overcome complications that ***specifically*** arise from neurotransplantations involving human dopaminergic neurons.

The Examiner relies on Galpern *et al.* as providing motivation to substitute human fetal spinal cord cells with porcine spinal cord cells. However, the teachings of Galpern

et al. are specific to neurotransplantation involving ***dopaminergic neurons***. The teachings of Giovanini and Galpern are directed to different populations of cells which are used to treat entirely different disease states. Therefore, one of ordinary skill in the art would not have extended the teachings of Galpern et al. beyond methods specific to treatment of Parkinson's disease. The Giovanini reference discloses the use of human spinal cord cells to treat acute resection or chronic contusion, while Galpern discloses the use of porcine ventral mesencephalic cells, which produce dopamine, to treat Parkinson's disease. The Examiner has failed to point to any teaching in the cited references which would motivate one of ordinary skill in the art to modify the teachings of Giovanini et al. by substituting the claimed porcine spinal cord cells for human spinal cord cells taught in that reference.

Furthermore, one of ordinary skill in the art would not have had a reasonable expectation of success in treating a spinal cord injury based on the combined teachings of Galpern and Giovanini. The teachings of Galpern focus on the ability of transplanted ventral mesencephalic cells to produce a factor. The ability of porcine VM cells to produce dopamine correlates with their ability to produce behavioral recovery (see page 7, column 1). The reference even teaches that cells genetically modified to produce dopamine (e.g., fibroblasts genetically modified to express the gene for tyrosine hydroxylase, see e.g., page 2 of the reference) may be able to be substituted for ventral mesencephalic cells. In contrast, the claimed methods are not based on the ability of porcine spinal cord cells to supply a missing factor. Therefore, the teachings of Galpern et al. regarding porcine VM cells, do not provide a reasonable expectation of success in using porcine cells of other types, such as the claimed spinal cord cells in transplantation.

However, in the interest of expediting prosecution of the application, the pending claims have been amended to require that the isolated spinal cord cells be obtained from an embryonic pig of between about 24 and about 35 days of gestation. Applicants teach that the use of cells from embryonic pigs in this age range leads to cell populations having improved properties. Specifically, as taught at page 9 of the specification, Applicants have found that connective tissue is not as easily separated from desired tissue when cells taken from animals less than about 24 days of gestation. Applicants have also

found that isolated spinal cord cells from fetuses older than about 35 days can have reduced viability. The specification teaches, e.g., at page 9, line 24, that the spinal cord cells of the invention are preferably taken from embryonic pigs in this age range. None of the cited art teaches the use of cells of this gestational age or their improved properties. Therefore, the cited art fails to teach or suggest all the claim limitations as required by M.P.E.P. 2143. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 17-21, 36, 39-45 and 47 be reconsidered and withdrawn.

Rejection of Claims 1, 8, 10-12, 15, 16, 18, 25, 26, 28-31, 33, and 34 Under 35 U.S.C. §103(a)

Claims 1, 8, 10-12, 15, 16, 18, 25, 26, 28-31, 33, and 34 are rejected under 35 U.S.C §103(a) as being unpatentable over Giovanini *et al.* in view of Galpern *et al.*, as applied to claims 1-4, 17-21, 36, 39-45, and 47, and in further view of Chappel. The Examiner relies on Giovanini *et al.* and Galpern *et al.* for the reasons set forth above, The Examiner states that Chappel teaches "that it was known in the art to alter MHC class I antigens on cells suitable for transplantation by using a combination of molecules to alter different epitopes on the same antigen for the purpose of reducing the immunogenicity of the cell." The Examiner also claims that it would have been obvious to one skilled in the art "to modify the immunogenicity of a population of embryonic porcine spinal cord cells for use in a xenogeneic transplantation method." Applicant respectfully traverses the rejection.

Applicant respectfully traverses the foregoing rejection on the basis that the Examiner has failed to establish a *prima facie* case of obviousness. Applicant respectfully submits that the claims are not obvious over Giovanini *et al.* and Galpern *et al.*, for the reasons set forth above with respect to the 103(a) rejection of claims 1-4, 17-21, 36, and 39-45 and 47.

Moreover, the secondary reference of Chappel *et al.* does not make up for the deficiencies in the primary references. The teachings of Chappel *et al.* are limited to the use of pancreatic islet, liver, neural, muscle, and hematopoietic cells. Chappel *et al.* teaches masking of two or more epitopes on cells to reduce immunogenicity during transplantation. Chappel *et al.* does not teach or suggest the specifically claimed compositions comprising an isolated spinal cord cell obtained from ***an embryonic pig of between about 24 and about 35 days of gestation***.

In view of the foregoing, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness in that the cited art fails to teach or suggest all the limitations of the claims. Accordingly, Applicant respectfully requests that this section 103(a) rejection be reconsidered and withdrawn.

Rejection of Claims 1, 5-7, 13 , 14, 18, 22-24, 31, 32, 35, 37 and 38 Under 35 U.S.C. §103(a)

Claims 1, 5-7, 13 , 14, 18, 22-24, 31, 32, 35, 37 and 38 are rejected under 35 U.S.C §103(a) as being unpatentable over Giovanini *et al.*, in view of Galpern *et al.*, as applied to claims 1-4, 17, 21, 36, 39-45 and 47, and in further in view of Fraser, Rosenbluth *et al.*, and Wang *et al.* The Examiner states that the references of Fraser, Rosenbluth *et al.*, and Wang *et al.* "were relied upon to teach that administration of specific cell populations, such as oligodendrocytes, astrocytes, and neural cells were known in the art to be suitable for xenogeneic transplantation of the into the spinal cord." Applicant respectfully traverses this rejection.

Applicant respectfully traverses the foregoing rejection on the basis that the Examiner has failed to establish a *prima facie* case of obviousness. Applicant respectfully submits that the claims are not obvious over Giovanini *et al.* and Galpern *et al* for the reasons set forth above with respect to the previous 103(a) rejections.

Moreover, the secondary references of Fraser, Rosenbluth *et al.*, and Wang *et al.* do not make up for the deficiencies in the primary references in that Fraser, Rosenbluth *et al.*, and Wang *et al.* do not teach or suggest Applicant's claimed compositions or methods, namely the references do not teach or suggest spinal cord cells derived from ***an embryonic pig of between about 24 and about 35 days of gestation***, as required by the pending claims.

In view of the foregoing, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness in that the cited art fails to teach or suggest all the limitations of the claims. Accordingly, Applicant respectfully requests that this section 103(a) rejection be reconsidered and withdrawn.

Rejection of 18-26, 28-37, 43, 44, and 46 Under 35 U.S.C. §112,First Paragraph

The Examiner has rejected claims 18-26, 28-37, 43, 44, and 46 under 35 U.S.C. §112, first paragraph. This rejection is respectfully traversed.

The Examiner states that the Applicant's arguments filed 4/23/01 are not persuasive because the Applicant has not limited the invention to "fetal porcine spinal cord cells." Applicant notes that the pending claims as amended each require that the porcine spinal cord cells be obtained from an embryonic pig of between about 24 and 35 days of gestation.

The Examiner further states that the specification "does not reasonably provide enablement for treating a xenogeneic subject having spinal cord damage resulting from the claim-designated neurodegenerative disorders, spinal cord injuries, or aging." The Examiner is of the opinion that the specification only provides enablement for treating spinal cord injuries in which the transplanted cells are implanted "at specific sites of damage (with respect to the hemi-sected model and the ALS model)." The Examiner further states that the specification provides no guidance for other types of spinal cord injuries. Applicant respectfully traverses the Examiner's rejection.

Applicant maintains that the specification provides ample support for use of porcine spinal cord cells for treatment of spinal cord damage, resulting from, e.g., spinal cord injuries or neurodegenerative disorders. Applicant respectfully submits that the teachings in the specification enable the treatment of a variety of different types of deficits that would benefit from transplantation of fetal spinal cord cells.

Applicant demonstrates ***both survival and integration of transplanted fetal porcine spinal cord cells***, upon transplantation into a subject. Thus, disorders that would benefit from survival and integration of transplanted fetal porcine spinal cord cells, such as those taught in the specification, or additional disorders known to one of ordinary skill in the art, would be treatable using the claimed compositions and methods.

Applicant teaches various ways by which spinal cord cells can be administered to treat such disorders. For example, Applicant provides working examples in which spinal cord cells were administered via grafting Gelfoam saturated with porcine fetal spinal cord cells into an immobilized spinal cord (see working example 2). In that example, rats which received the transplanted cells demonstrated transplant-mediated reestablishment of host spinal tracts on the cellular level as determined by measuring supraspinal serotonergic (5-HT) innervation and axonal projections from the dorsal root ganglia using calcitonin gene-related peptide (CGRP) as a marker. For example, cells can be administered by transplanting Gelfoam saturated with porcine fetal spinal cord cells into the spinal cord or by administering to one side of the spine at lumbar level L1 in the ventral horn of the spinal cord (see e.g., page 13 line 19 to page 22, line 4 of the specification). Applicant further teaches that, "a common method of administration of cells into the spinal cord of a subject is by direct stereotaxic injection of the cells into the area of spinal cord damage as well as sites rostral and caudal to that area" (page 14, lines 1-4). Further support can be found on page 14, lines 14-39. Applicant also provides exemplary numbers of cells to transplant. Furthermore, behavioral data obtained from tests such as contact placing reflex, open field, inclined plane, beam walking, righting

reflex, grasping reflex, and locomotor behavior, demonstrates the beneficial effects of the grafts at the ***functional anatomical level***. Applicant also teaches, e.g., in Example III, ***successful treatment*** of SOD mice (a model of ALS) by transplanting fetal porcine spinal cord cells into the ventral horn of the spinal cord.

Thus, Applicant has demonstrated survival and integration of transplanted cells, has provided working examples of the treatment of two types of spinal cord damage by transplantation of fetal porcine spinal cord cells (i.e., damage due to physical trauma to the spinal cord and damage due to a progressive neurodegenerative disease). Applicant notes that even for spinal cord damage involving demyelenation, areas of damage tend to be focal and, therefore, the methods of administration taught in the specification are appropriate for treating numerous types of spinal cord damage. Applicant submits that the specification provides sufficient teaching to enable the treatment of various kinds of spinal cord damage that would benefit from the survival and integration of porcine spinal cord cells. It is Applicant's position that one of ordinary skill in the art would be able to treat the claimed disorders for treatment without undue experimentation, particularly given the working Examples presented in the specification.

The Examiner is further of the opinion that "the specification does not disclose where the spinal cord cells should be administered, whether the spinal cord cells are a heterogeneous or homogeneous population of cells, the amount of spinal cord cells to be administered, or the age of the cells to be administered, *i.e.*, the time during embryonic development in which the cells were isolated."

In contrast, Applicant teaches exemplary cell compositions and methods of administering such compositions. The spinal cord cells of the invention are described in the instant specification (see, e.g., least at page 8, lines 17-32) where Applicant teaches that spinal cord cells are porcine embryonic cells and which display the desired characteristics for transplantation. Applicant further teaches that, "a common method of administration of cells into the spinal cord of a subject is by direct stereotaxic injection of

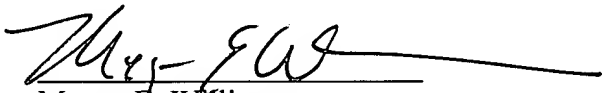
the cells into the area of spinal cord damage as well as sites rostral and caudal to that area" (page 14, lines 1-4). As set forth above, Applicant notes that even for spinal cord damage involving demyelenation, areas of damage tend to be focal and, therefore, such methods of administration are appropriate for treating numerous types of spinal cord damage. Applicant also points out that the claims as pending do not require that the compositions be homogeneous, in fact, in one embodiment, glial cells can be present. Applicant further teaches age ranges for pigs from which cells can be isolated (see, e.g., page 9 of the specification). Applicant also provides exemplary numbers of cells that can be administered. In addition, optimal numbers of cells can readily be determined by one of ordinary skill in the art using no more than routine experimentation. Armed with the teachings in the specification one of ordinary skill in the art could readily treat a variety of different disorders using the claimed compositions or methods.

The Examiner claims that the specification only enables a method of treatment for "spinal cord damage as observed in the animal model of amyotrophic lateral sclerosis (ALS) or hemi-sected animal model." However, Applicant submits that these models were used merely as examples to demonstrate the transplantation of embryonic porcine spinal cord cells and as set forth above, the teachings of the specification can be applied to various types of spinal cord damage. Therefore, the described animal models should not be used to limit the claimed invention as suggested by the Examiner. Applicants further note that claim 36 is specifically directed to the treatment of spinal cord injury. Claim 38 is specifically directed to the treatment of ALS. Therefore, these claims are specifically directed to the two types of spinal cord damage exemplified in the specification. Accordingly, it is Applicants' position that the instant 112 rejection should not apply to these claims or the claims which depend therefrom.

CONCLUSION

In view of the amendments and remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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Version With Markings To Show Changes Made

1. **(Amended)** A composition for transplantation into a mammalian xenogeneic subject comprising isolated spinal cord cells obtained from [a] an embryonic pig of between about 24 and about 35 days of gestation, such that treatment of spinal cord damage that would benefit from survival and integration of the spinal cord cells is obtained upon transplantation into the subject.

3. **(Amended)** The composition of claim [2]1, wherein the spinal cord cells are isolated from an embryonic pig between about days 24 to 30 of gestation.

4. **(Amended)** The composition of claim [3] 1, wherein the spinal cord cells are isolated from an embryonic pig between about days 25 to 29 of gestation.

10. **(Amended)** The composition of claim 8, wherein the [cell] cells are contacted prior to transplantation into the xenogeneic subject with at least one anti-MHC class I antibody or fragment thereof, which binds to the MHC class I antigen on the cell surface but does not activate complement or induce lysis of the cells.

18. **(Amended)** A method of treating a mammalian xenogeneic subject having spinal cord damage that would benefit from survival and integration of porcine spinal cord cells by administering to the subject a composition comprising isolated spinal cord cells obtained from [a] an embryonic pig of between about 24 and about 35 days of gestation, such that treatment of spinal cord damage is obtained upon administration of the composition to the subject.

20. (**Amended**) The method of claim [19]18, wherein the spinal cord cells are isolated from an embryonic pig between about days 24 to 30 of gestation.

21. **(Amended)** The method of claim [20] 18, wherein the spinal cord cells are isolated from an embryonic pig between about days 25 to 29 of gestation.

36. **(Amended)** The method of either of claims 1 or [claim] 18, wherein spinal cord damage is spinal cord injury.